Opinion Paper

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Point-of-care testing: state-of-the art and perspectives

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Abstract: Point-of-care testing (POCT) is becoming an increasingly popular way to perform laboratory tests closer to the patient. This option has several recognized advantages, such as accessibility, portability, speed, convenience, ease of use, ever-growing test panels, lower cumulative healthcare costs when used within appropriate clinical pathways, better patient empowerment and engagement, and reduction of certain pre-analytical errors, especially those related to specimen transportation. On the other hand, POCT also poses some limitations and risks, namely the risk of lower accuracy and reliability compared to traditional laboratory tests, quality control and connectivity issues, high dependence on operators (with varying levels of expertise or training), challenges related to patient data management, higher costs per individual test, regulatory and compliance issues such as the need for appropriate validation prior to clinical use (especially for rapid diagnostic tests; RDTs), as well as additional preanalytical sources of error that may remain undetected in this type of testing, which is usually based on whole blood samples (i.e., presence of interfering substances, clotting, hemolysis, etc.). There is no doubt that POCT is a breakthrough innovation in laboratory medicine, but the discussion on its appropriate use requires further debate and initiatives. This collective opinion paper, composed of abstracts of the lectures presented at the two-day expert meeting "Point-Of-Care-Testing: State of the Art and Perspective" (Venice, April 4–5, 2024), aims to provide a thoughtful overview of the state-of-the-art in POCT, its current applications, advantages and potential limitations, as well as some interesting reflections on the future perspectives of this particular field of laboratory medicine.

Keywords: point-of-care (POCT); advantages; limitations; applications

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Laboratory medicine: POCT and the brain-to-brain loop

Point-of-care testing (POCT) has been defined as a "medical testing at or near the site of patient care by healthcare professionals" [1]. The term "specially trained" can be added to "healthcare (non-laboratory professionals)" to recognize the evidence that most errors in POCT were and, possibly, are still due to the lack of knowledge or non-compliance with standard operating procedures [2]. However, a narrower definition of POCT is "testing performed by the patients themselves" [3]. While the former definition may maintain POCT within the traditional brain-to-brain loop [4], the latter seems to characterize POCT as a direct-to-consumer testing (DTCT), thus changing the traditional framework which characterizes the relationships between laboratory professionals and physicians. In the new scenario, POCT should be used as a type of self-sampling and self-testing approach and, therefore, may require further concern. The core principle underlying POCT measurements has been described as "reducing the turnaround time (TAT) without compromising the quality of information". Therefore, careful evaluation of analytical quality performances should be always performed when adopting POCT in clinical practice. Analytical performance specifications (APS) have been defined as "the level of performance required to facilitate clinical decision-making", but if POCT is becoming a type of DTCT, even APS should be revised because customers cannot understand and appreciate the quality of results and the ultimate consequences for diagnosis and therapy. The evolving trend towards decentralized laboratory testing requires major concern, avoiding uncontrolled approaches and recommending an appropriate governance by laboratory professionals.

This collective opinion paper, composed of abstracts of the lectures presented during the two-day expert meeting "Point-Of-Care-Testing: State of the Art and Perspective" (Venice, April 4–5, 2024), aims to provide a thoughtful overview of the state-of-the-art in POCT testing, its current applications, advantages and potential limitations, as well as some interesting reflections on the future perspectives of this particular area of laboratory medicine (Table 1).

Table 1: Summary of the lectures of the International Point-of-Care Testing: State-of-the art and perspectives.

Session I – Technologies and quality in POCT
Chairpersons: A. Khan (Philadelphia, USA), J. Nichols (Nashville, USA)
09.00 a.m. – 09.45 a.m. Keynote lecture: Laboratory medicine: POCT and the brain-to-brain loop. M. Plebani (Padova, Italy)
09.45 a.m. – 10.15 a.m. POCT: state of the art for meeting patient needs in new ways. J. Nichols (Nashville, USA)
10.15 a.m. – 10.45 a.m. Emerging POCT technologies. P. Luppa (Munich, Germany)
10.45 a.m. – 11.15 a.m. Data driven approaches to improve the quality of home collected specimens. D. Greene (Seattle, USA)
11.45 a.m. – 12.15 p.m. Quality systems and accreditation. L. Sciacovelli (Padova, Italy)
12.15 p.m. – 12.45 p.m. Quality Indicators for POCT. J. Shaw (Ottawa, Canada)
12.45 p.m. – 01.15 p.m. Professional training and certification in POCT. A. Khan (Philadelphia, USA)
Session II – POCT in different clinical settings
Chairpersons: A. Antico (Bassano del Grappa, Italy), M. Ciaccio (Palermo, Italy)
02.30 p.m. – 03.00 p.m. POCT in critical care P. Carraro. (Padova, Italy)
03.00 p.m. – 03.30 p.m. Continuous glucose monitoring. G. Freckmann (Ulm, Germany)
03.30 p.m. – 04.00 p.m. POCT in disaster situations. G. Lippi (Verona, Italy)
04.00 p.m. – 04.30 p.m. POCT in infectious diseases: lessons from the Covid-19 pandemic. W. Dimech (Victoria, Australia)
05.00 p.m. – 05.30 p.m. POCT and cardiovascular diseases: a moving target. M. Zaninotto (Padova, Italy)
05.30 p.m. – 06.00 p.m. POCT in hemostasis and thrombosis. M. Spannagl (Munich, Germany)
06.00 p.m. – 06.30 p.m. POCT in molecular and genetic diagnostic. J. Huggett (Surrey, UK)
Session III – POCT and the healthcare system
Chairpersons: M. Chiozza (Padova, Italy), P. Luppa (Munich, Germany)
09.00 a.m. – 09.45 a.m. Keynote lecture: Laboratory medicine: global warming: why, when, how and where we should implement point of care strategies. G.J. Kost (Davis, USA)
09.45 a.m. – 10.15 a.m. POINT OF CARE TESTING (POCT) and evidence based laboratory medicine (EBLM) does it leverage any advantage in clinical decision making? T. Trenti (Modena, Italy)
10.15 a.m. – 10.45 a.m. Artificial intelligence as an integration tool. A. Padoan (Padova, Italy)
10.45 a.m. – 11.15 a.m. Innovative laboratory testing strategies to complement telehealth demand. D. Greene (Seattle, USA)
11.45 a.m. – 12.15 p.m. POCT and pre-analytical quality. G. Lippi (Verona, Italy)
12.15 p.m. – 12.45 p.m. An innovative approach to quality assurance for POCTS. W. Dimech (Victoria, Australia)
Session IV – from now to the future
Chairpersons: F. Curcio (Udine, Italy), M. Plebani (Padova, Italy)
02.00 p.m. – 02.30 p.m. Repeat testing and prevalence boundaries the mathematics of covid-19 rapid antigen tests. G.J Kost (Davis, USA)
02.30 p.m. – 03.00 p.m. POCT in pharmacies and decentralized testing sites. F. Curcio (Udine, Italy)
03.00 p.m. – 03.30 p.m. POCT and laboratory networks. A. Thomas (Cardiff, UK)
03.30 p.m. – 04.00 p.m. Role of POCT in value-based laboratory medicine. G. Banfi (Milano, Italy)

Point-of-care testing: state of the art for meeting patient needs in new ways

POCT is an increasingly popular means of conducting laboratory testing closer to the site of patient care [5]. POCT provides rapid turnaround of test results with the potential for more rapid clinical action that can improve patient outcomes [6]. Portability, ease-of-use, and minimal training requirements are some of the advantages of POCT. The convenience of testing closer to the patient is opening a variety of opportunities to provide healthcare in the community outside of hospitals and physician office clinics. Companies are marketing POCT devices to patients for home self-testing and through home collection kits with direct-access testing. Pharmacy walk-in clinics and doctor-on-call services provide more convenient means for patients to see a clinician without having to wait for an appointment from their primary care physician. The patient is in the driving seat, taking charge of their health and demanding healthcare services that meet their needs, at their convenience and timeframe. The coronavirus diseases 2019 (COVID-19) pandemic has opened new opportunities for telehealth, hospital-at-home, and concierge medicine services that require faster test result TAT. The future of POCT promises new sensors, wearable devices and smart technologies that are less invasive and can better connect the patient with their physician. The convenience and ease-of-use of POCT will find new applications and develop novel ways that laboratory diagnostics can improve patient outcomes in the future.

Emerging POCT technologies

The development of novel analytical techniques is the driving force to improve the diagnostic efficiency of POCT methods [7]. Currently, there are two prominent new disruptive technologies, already implemented in clinical routine, which significantly helped to increase the market share of POCT to more than 30 % of the total *in vitro* diagnostics market in the last five years. One development is the now widespread continuous glucose monitoring (CGM). The 24 h-monitoring mode of the interstitial glucose concentration has led to tremendous clinical improvements, as shown by the significant lowering of HbA_{1c} and reduction in the number of hypoglycemic events in adults with diabetes [8]. The second important analytical novelty is the establishment of cartridge-based POCT-devices for detection of nucleic acids of infectious agents. The cartridges ensure a stringent extraction of bacterial or viral DNA/RNA, followed by PCR or isothermal amplification step. Simultaneously they prevent cross-contaminations of nucleic acids. These so-called Nucleic Acid Testing (NAT) systems for identification of infectious agents have the great potential to bridge the diagnostic gap between centralized laboratory services and emergency departments. On-site monitoring and control management of the outbreaking of infection events can speed-up the diagnosis and treatment of infected patients. Emerging technologies for POCT devices will use innovative recognition elements, improved signal generation, miniaturization and innovative networking as well as sophisticated surface chemistries. Challenges for these technologies include (i) the search for novel disease markers, as clinical need is seen in the early identification of (chronic) diseases, still in a treatable stage; (ii) robustness of the methods, as the preanalytical phase must be uncomplicated and analytics traceable; (iii) gain of diagnostic information must be ensured for the biochemical/genetic testing compared to imaging techniques. Examples for promising developments are aptamers, as versatile alternative recognition elements compared to antibodies and nanoparticles (NPs) for advanced signal generation. Nobel metal nanoparticles (NPs), rare earth upconverting NPs, as well as hollow mesoporous Janus Si-NPs are engineered nanomaterials to be successfully used in POCT assays [9].

Home collected samples to support telehealth services

As demand for and access to telehealth services increases, the laboratory should be prepared to support these models of healthcare [10]. Ideally, laboratories can develop test menus that are analytically and clinically appropriate for home collection of specimens with postal carrier transport to a regional laboratory location. This model is ideal for non-acute care and for sample types/analytes that are stable for transport.

In this session of the article, discussion will be made on sample types that are amenable to home collection, including swabs, saliva, urine, stool, and capillary blood, indicating that the latter can be collected into microvette containers or spot onto filter paper and dried. We also discuss here data driven approaches to improve the quality of home collected specimens. For example, a reflex algorithm has been illustrated to identify erroneously elevated total testosterone concentrations [11]. Topical testosterone contamination is more likely to happen if patients are self-collecting their samples from finger sticks, but if contamination was suspected, the illustrated algorithm could be appropriate for any laboratory, regardless of where the

specimen was collected. Further, testosterone overuse is also more common in patients collecting samples from home, as evidenced by comparing the frequency of supra-physiological results between an academic medical center and a direct-access-testing company. Lastly, a corrective action following failed proficiency testing must be highlighted, whereby matrix matched calibrations were necessary for accurate lead screening results [12].

The second part of this session presents innovative laboratory testing strategies to complement telehealth demand and focuses on developing accessible sexually transmitted infections (STI), chronic kidney disease (CKD), and cervical cancer screening. Here we discuss the need for remote sample collection for STIs that are inclusive of sexual behaviors [13], and highlight the potential for primary cervical cancer screening recommendations to be satisfied with home collected swabs [14]. Additionally, data validating dry blood spots for creatinine quantification and data supporting a decreased lower limit of quantitation for urine albumin illustrate that home collection options should be explored to address CKD screening deficiencies [15, 16]. Historically, the only home collection kits that laboratories have offered to patients have been for stool in colorectal cancer screening. The laboratory community should develop remote collection strategies for additional testing pathways to compliment the evolving nature of virtual medicine.

Quality system and accreditation

In the context of the management of POCT the implementation of a suitable Quality Management System (QMS) recognized through an accreditation process, that complies with international standard requirements, supports laboratory professionals in ensuring a high level of performance quality [17]. However, the effectiveness of these important tools, QMS and accreditation process used in laboratory medicine depends on the awareness level achieved by laboratory professionals regarding their importance and suitable application in the context of the mission of laboratory medicine. Concerning POCT, the suitability of results is crucial because medical decisions are taken immediately after testing, leaving little room for result correction. Scientific literature has demonstrated that the most frequent errors occurring during the use of POCT can arise in all activities of the process. The implementation of a suitable QMS establishes conditions to ensure that the quality of tests can assist clinicians in better patient management, providing increasingly reliable test results and reduced errors, also thanks to identification of suitable performance specifications. It should allow, for example, accurate management of procedures for operator continuous training, verification of *in vitro* diagnostic system devices, development of competency, and appropriate use of quality assurance tools (Internal Quality Control [IQC], External Quality Assessment [EQA] schemes, Quality Indicators [QI] etc.). Adherence of QMS to the International Standard for Accreditation of medical laboratories, the ISO 15189, guarantees its well-structured implementation, instills confidence in laboratory and POCT results and advances patient care. The standard ISO 15189 specifies requirements for quality and competence in medical laboratories and POCT, ensuring compliance with high-quality specifications, fosters professional competence and interdisciplinary collaboration. In the last edition issued in 2022, it includes POCT requirements of the previous specific International Standard for POCT, the ISO 22870 [18], that is no longer available. It is applicable when the POCT is carried out in hospitals, clinics and by a healthcare organization providing ambulatory care; it is not applicable for patient self-testing at home.

The standard promotes the use of the most important tools for monitoring the quality of performance, such as the use of IQC for monitoring stability of analytical examination; the participation in an EQA Program, to keep under control the accuracy of analytical results; and the use of QI, to keep under control the undesirable events occurring in the activities of the total testing process. In conclusion the achievement of ISO 15189 accreditation ensures a high-quality of medical laboratory and POCT performance because all activities are correctly and effectively implemented and monitored within a well-structured QMS and a high competence of personnel is continuously promoted [19, 20].

Quality Indicators for POCT

A good QI is one that represents a key part of the testing process, is measurable and for which data is readily accessible, ideally electronically. QI must be measured against a benchmark. The Canadian Society of Clinical Chemists (CSCC) POCT and QI special interest groups recently published recommendations for establishing quality QI for glucose POCT [21]. The steps in the glucose POCT process deemed highest risk were mapped out by consensus of the authors. These included pre-analytical, analytical and post-analytical steps. A risk assessment was performed for each step identified. The risk assessment criteria were probability of failure, consequence of failure and chance of detecting the error.

Positive patient identification (PPID) was identified as a high-risk pre-analytical step. This indicator was included in the Quality Indicator program of the Societe Quebecoise de Biologie Clinique (SQBC) and laboratories from across Canada were asked to submit data for a one-month period.

Laboratories (n=57) submitted the total number of POCT glucose tests performed during that month and the number of tests that were performed without a valid patient identifier. There was a higher rate of compliance with PPID in sites where glucose meters were connected to the electronic health record for results transmission [22]. Repeat of critically high POCT glucose results was identified as a high-risk post-analytical step. Data from the CSCC POCT/QI working group member sites demonstrated a high rate of discordant results when critically high POCT glucose results are repeated. This exemplifies the importance of repeating critically high results before taking clinical action. Data from The Ottawa Hospital found the most common reasons for discordant results to be insufficient hand washing prior to the test and contamination of specimens taken from a line [22].

Quality control failures were chosen as an analytical QI to monitor as the data are accessible electronically. Data collected for a one-month period from working group member sites (n=22) were asked to submit the total number of quality control (QC) performed and the number of QC points outside the acceptable limits for the time period. Vial switches (low and high QC) accounted for most QC failures, ranging between 33 and 72 %. Some high-risk steps of the glucose POCT process are not amenable to monitoring as QI, and are better suited to monitoring via audits. Examples include washing of patient hands, wiping away the first drop of blood, storage of reagents, labeling of reagents and instrument cleaning.

Professional training and certification in POCT

POCT is the fastest growing sector of laboratory medicine because it allows either self-testing or patient testing at the point-of-care with devices that are portable, easy to use, require very little troubleshooting and generate either a qualitative (positive/negative) or a quantitative test result in seconds to minutes. As a result, it is used in hospitals, physician offices, pharmacies, community centers, nursing homes or disaster areas. Hence, users of POCT range from healthcare workers to student volunteers, and many of these have no or limited training in laboratory medicine and therefore may not understand the rationale behind quality control testing and other quality assurance practices [23].

To manage healthcare workers with different skills and knowledge on laboratory tests, the POCT Coordinator needs to have a variety of skill sets. In the United States, the POCT Coordinator's role is well established – the Association of Diagnostics and Laboratory Medicine (ADLM) (formerly known as the American Association for Clinical Chemistry (AACC)) has a POCT Specialist Certification Program. In other countries however, there is a POCT Coordinator shortage and often there is no guidance or job description on their role in the laboratory and healthcare services.

The POCT Specialist Certificate Program is built upon the skill sets that a POCT director and coordinator need to have so they can perform their job properly. These subject areas include regulations, quality management, policies and procedures, instrument selection and validation, connectivity and Information Technology (IT), education and training, and administration. As well as the POCT Coordinator and Director, healthcare workers also need to be educated by a designated trainer that is knowledgeable on the test. Therefore, professional training and certification in POCT provides a framework to ensure that healthcare workers deliver high levels of patient care, consistently – in a standardized manner, with the aim of creating a cohesive, and well-trained team. Thus, certification improves patient care and outcomes.

POCT in critical care

The highest quality level for laboratory testing is obtained by the institutional laboratory, when adopting procedures and methodologies where competence, selection of methods and operational control are the results of years of experience. In addition, the throughput aspect allows us to consider the laboratory as the place for these activities. On the other hand, the benefits of decentralization include operational simplification, in particular of the pre-analytical phase, and the immediacy of test results, which would not be achievable with traditional methods. This statement, in turn, leads to consider the disadvantages: in the institutional laboratory, TAT for critically ill patients are often insufficient, and the waste of blood may even produce iatrogenic anemia. With POCT, among all other limitations, costs must be considered, as they are often higher, in addition to the evidence that tests are performed by non-professional staff. Therefore, the value of timeliness seems to be counterbalanced by the value of reliability. Furthermore, we must consider the specificities of the clinical environment; for example, the context of the intensive care unit (ICU) and the emergency room, where time is more important than in other clinical settings. However, safety and reliability of data are also crucial, as clinical decisions are immediate and cannot wait for verification or cross-validation. In the ICU there are now many new needs: shorter analytical times, IT integrations, portability of instruments with data to the patient's bedside, and ever greater analytical quality.

In the past, we showed the high risks associated with lack of connectivity of POCT instrumentation, in particular

those related to the manual transcription of results [24]. We estimated and described the risk of error when glycemia results are manually transcribed from the instrument display as, in approximately 3 % of cases, data contained in the patients' clinical records were incorrect concerning the time of determination or the concentration. Of these, a fraction of about 7 % could lead to insulin dosing errors [24]. Even in an ICU, we reported a high frequency of transcription errors in blood gas analysis.

In this recent survey, cases with excess differences of more than 1 g/dL for hemoglobin were 1.43 %. Of course, not all of these cases were due to analytical errors, but they represent a QI highlighting the need for continuous retraining of POCT staff. In another recent experience conducted at the Public Hospital of Venice we recorded some safety observations related to a POCT system active during the night hours in the emergency room. Since July 2023 we have activated an accurate study, every morning just after the end of the POCT use, which consisted of critically re-evaluate the results, verifying the management of critical values, rerun tests with warning signals, and analyze particular cases. The problems detected were non-recognition of hemolyzed, coagulated samples or other interferences, the failure to repeat very abnormal values, inability to dilute samples but, primarily, there was a lack of critical discussion with the reference laboratory scientist in cases that needed to be investigated. The added value in healthcare is people more than technologies, and first and foremost, professional skills. The path to follow must consider the creation of multidisciplinary teams, in particular with the world of critical care and colleagues from the Society of Critical Care Medicine call us for better cooperation, adopting a humanistic approach [25]. Current developments in informatics may lead to better integration between computer systems to overcome the separation between clinical monitoring, laboratory data, pathology, imaging, and cardiac and endoscopic investigations to eventually adopt artificial intelligence (AI) and machine learning tools to provide an integrated diagnostic report.

Continuous glucose monitoring

Continuous glucose monitoring (CGM) is recommended for all people with diabetes on insulin therapy. In contrast to traditional self-monitoring of blood glucose, CGM measures glucose continuously in the interstitial fluid and generates complete glucose profiles. Data obtained by CGM are increasingly used to not only complement but also to guide diabetes therapy. Additionally, CGM-derived metrics such as time in range (TR) have evolved which are currently discussed to even replace HbA_{1c}. Despite the increasing use of CGM and in contrast to blood glucose monitoring systems (ISO 15197), there is no international standard that defines acceptance criteria and study procedures for evaluation of CGM. As a consequence, it is very difficult to compare the performance of CGM systems tested in different studies, and the reported accuracy of available CGM systems is highly variable [26]. Furthermore, CGM-derived metrics such as TR can be different depending on the CGM system used. With regard to the clinical use and importance of CGM, there is a strong need for standardization. Therefore, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) founded the working group on CGM (WG-CGM) in 2019 that is concerned with this topic. The first goal of WG-CGM was the definition of traceability of CGM measurements, concluding that CGM systems are currently not adequately traced to higher-order standards or methods [27]. The second goal was to propose study procedures which mainly aim at obtaining values in all clinically relevant glucose ranges and sufficiently high rates of change in order to reflect real-life use of the systems and to also cover extreme cases [28]. In addition, quality of the comparator method is crucial for apparent accuracy of a CGM system and needs to be ensured by meeting defined analytical performance criteria [29]. The ultimate goal of the WG-CGM is to define metrics and accuracy criteria to serve as the basis for a future ISO standard, because only if testing procedures for CGM performance studies are standardized and well-designed, results for different CGM systems can be compared and interpreted independently.

POCT in disaster situations

A natural hazard is traditionally seen as a threat from an adverse event that could have a negative impact on humans or the environment, while a natural disaster is the transformation of the hazard into a real tragedy for humanity, leading to environmental, social and economic disruption. The causes of natural disasters are numerous and sometimes interrelated; they include land movements (e.g., avalanches, earthquakes, volcanic eruptions), water (e.g., floods, tsunamis) and weather (e.g., tornadoes, blizzards, hurricanes, droughts, hailstorms, heat waves) disasters, fires, epidemics, pandemics, famines, space interference (gamma ray bursts, impacts, solar flares) and anthropogenic disasters such as wars, industrial disasters, bioterrorism and cyberterrorism [30]. Collectively, these massive disasters have led to the coining of the term "newdemics" to describe unexpected and disruptive problems that affect the health of large numbers of people in a crowded world [31].

Apart from general healthcare issues (i.e., providing food, water, sanitation, electricity and public transportation to healthcare facilities), the key question is obvious: is laboratory medicine ready for this challenge? We have learned from the

past that health services and laboratory medicine may be underprepared for these challenges, as various problems may arise, such as the lack of laboratory equipment in the post-operative centers of mobile hospitals, but also the lack of coordination of equipment, supplies, physicians, laboratory technicians and other medical staff that may be transferred from elsewhere. Knowing that the immediate response depends on the nature and severity of the natural disaster, the environment and its conditions, the local organization of the healthcare system and its level of preparedness, some actions can be taken immediately after the event. These include, (i) damage assessment to restore, reactivate and reorganize the laboratory network, (ii) integration of trained laboratory personnel into rapid response brigades, (iii) equipping brigades with portable laboratories and supplies for on-site testing and sampling, and (iv) close coordination of activities with the national disaster and epidemiology programs. To this end, the organization of disaster laboratory facilities may include (i) preparing existing laboratory facilities to provide emergency services, whenever possible, (ii) creating temporary stationary laboratory facilities in existing rooms, tents, or purpose-built shelters near the health center, (iii) constructing mobile laboratories in some form of transportation such as trucks, vans, trailers, rail cars, planes or boats, and (iv) equipping personnel with self-contained diagnostic systems that are easily carried (even by drones, for examples), compact, and relatively lightweight. POCT devices have several features that make them particularly suitable for disaster response: they are portable, internally battery-powered, relatively robust analytically and work with simple disposable reagent cartridges. There are also some specific rules for performing POCT in disaster situations. These include the appointment of a POCT coordinator, decisions on urgent import or extension of POCT, and appropriate training of new users on pre- and post-examination activities. A minimum set of vital tests may also be suggested, including complete blood cell count, aminotransferases, lipase, glucose, creatinine, electrolytes, cardiac troponins, blood gas analysis, prothrombin time, D-dimer and some selected infectious disease tests. The main challenges to the correct functioning of POCT in an otherwise unnatural and hostile environment include patient and specimen identification, training, allocation, temperature (too hot or too cold), humidity and continuous reagents availability.

POCT in infectious diseases: lessons from the COVID-19 pandemic

Localized outbreaks of infectious diseases occur frequently, with recent examples being Zika and West Nile Virus in the Americas, Ebola in Africa, Middle East Respiratory Syndrome (MERS) in the Middle East and Dengue and Chikungunya in Asia. However, the recent severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) pandemic demonstrated how disruptive a global outbreak can be, and highlighted inadequate processes counties had in responding to such a threat, in particular in the regulation of test kits or *in vitro* diagnostic devices (IVDs). Prior to the pandemic, IVD regulation was somewhat harmonized globally, with the devices categorized by the risk posed to the individual and the public [32]. Those IVD of highest risk such as those used to diagnose HIV or hepatitis are categorized as Class D in Europe (or Class 4 in Australia) and low risk devices such as chemicals and stains as Class A (Class 1) [33]. The evidence that manufacturers are required to provide to regulators prior to licensing of their use is proportional to their risk. As an example, HIV test kits required sensitivity and specificity to be estimated using 300 highly characterized positive and more than 500 negative samples as well as at least 20 seroconversion panels [34].

Given the urgency for diagnostic testing at the beginning of the pandemic, regulatory bodies globally instituted the Emergency Use Listing (EUL). This required manufacturers to maintain ISO 13485 accreditation for manufacturing, but provide minimal test kit performance data, much of which was accumulated by the manufacturer [35]. The consequence of reducing the barrier to entry of new IVD manufacturers was that, by June 2020, more than 700 SARS-COV-2 IVDs were available on the market, many of which were developed and sold by manufacturers new to infectious diseases and the normal regulatory process. Manufacturers were faced with competition for raw materials such as plastics and biological components e.g., Taq polymerase, disruption of supply chain and the need to ramp up manufacturing of a novel product. Immature quality systems and lack of regulatory oversight, along with government competition for products lead to the purchase and use of IVDs that were not fit for purpose.

Regulatory authorities generally did not require IVDs to be assessed post-market, leaving the assessment to already stretched laboratories, poorly equipped to evaluate IVDs. This situation results in poorly constructed and inadequate evaluations, misinterpretation of data and conflicting evaluation results. Fortunately, some government-funded evaluations were published in a timely manner to provide objective evidence of IVD performance. The National Serology Reference Laboratory, Australia (NRL) was funded by the World Health Organization (WHO) to perform evaluations on 35 SARS-COV-2 serology rapid diagnostic test (RDT) kits [36], with a subsequent evaluation of 25 automated assays [37]. Significant differences in performance were identified. NRL, in collaboration with the Peter Doherty

Institute, also performed analytical sensitivity assessment of 92 RDTs for SARS-COV-2 antigen tests funded by the Therapeutic Goods Administration. Of these six were found to be non-compliant.

In May 2023, the WHO declared the end to the COVID-19 pandemic. Since then, regulators have normalized the regulatory process for SARS-COV-2 IVDs, requiring performance evidence. In Europe the tests are classified as Class D, whereas in Australia they are Class 3. However, we are not ready to face a new pandemic [38]. To do so, governments need to fund organizations with test kit evaluation experience to establish material transfer agreements and templated evaluation protocols, obtain ethics, create relationships with clinical services to collect samples in adequate numbers and volumes, and to facilitate the international importation of infectious disease materials and tests.

POCT and cardiovascular diseases: a moving target

POCT in cardiovascular diseases may be considered a moving target, first from the clinical point of view. In fact, cardiovascular diseases and in particular myocardial infarction, are included in the top 15 individual diseases that are associated with the greatest number of serious misdiagnosis-related harm in the emergency department [39]. In the last 20 years, cardiac troponins have been identified as the gold standard not only for diagnosing acute cardiac diseases, but also to detect myocardial injury thanks to the development of high sensitivity methods which have changed the previously described clinical scenario. The measurement of cardiac troponins, in fact, is currently recommended in all clinical and laboratory medicine guidelines, because their prevalent features are the typical kinetic release and well-defined analytical performance [40]. In addition, a second moving target from a clinical point of view related to disease management in the emergency department is represented by acute heart failure, the most frequent cause of unplanned hospital admission in patients aged above 65.

All guidelines define acute heart failure as new onset or worsening of symptoms, associated with elevation of natriuretic peptides, which are a biochemical standard to differentiate the origin of dyspnea [41]. From several years POCT for natriuretic peptides measurement are available in emergency setting, to meet the clinical guidelines recommendations, suggesting their measurement in different clinical settings not only for the diagnosis but also for the prognosis and risk stratification in patients with suspected heart failure. However, in the real world, not only the POCT for natriuretic peptides is poorly adopted, but several concerns exist about the real usefulness as demonstrated by the results of a survey carried out among general practitioners [42]. For this reason and in order to broaden the potential of natriuretic peptides measurement in primary care, a “3 A” strategy has been proposed that includes: Awareness (of heart failure as a public health topic); Access (enable the opportunities to diagnose heart failure in primary care); Adoption (assuring that testing is adopted in all patients because now there is no or partial access to the specific test in several countries) [43]. Analytical improvement in POCT for cardiac troponins seems to be particularly relevant in order to adopt the so-called accelerated algorithm, and in particular the serial measurement at time 0 and 1 h after the admission to the emergency department, as suggested by recently published guidelines [43]. The availability of high sensitivity POCT for troponins, therefore, may represent a relevant progress not only for the typical rapid TAT, but also for the possibility to decentralized diagnosis of myocardial injury in different clinical settings. For example, a new field of interest is the adoption of troponins POCT in ambulances, allowing pre-hospital management of patients, early risk stratification and optimization of clinical pathways and resources. In conclusion, this moving target has finally come to a standstill: actually, there are commercially available POCTs showing analytical performance of high sensitivity methods that provide additional value in terms of shorter length of stay in the emergency department, reduction of the time to treat, and increased number of discharges. However, as expected at the beginning of the use of new devices in clinical practice, some concerns remain, including the need to implement a quality system ensuring IQC and EQA in whole blood, and a strategy to harmonize the results from different assays (such as those from POCT and central lab in patients admitted to the same hospital). Finally, considering the epidemiological and clinical importance of cardiovascular disease, the trend may be towards a bloodless transdermal measurement of cardiac troponin I based on molecular spectroscopy that in a near future could be the new goal [44].

Coagulation testing at point of care (POC)

For reasons of standardization and practicability, coagulation testing in the central laboratory uses blood plasma or serum as the analytical matrix. On the other hand, the need for simplicity and speed leads to the analysis of whole blood at the point of care. The most widely used whole blood

coagulation test is the activated clotting time (ACT) for the monitoring of unfractionated heparin. By methodological standards the ACT is – similar to the activated partial thromboplastin time (aPTT) – a rather poor assay, still it is successfully used internationally since decades. Another method applied in the management of coagulopathy at the point of care is viscoelastometry, which provides an overview over coagulation activation, mechanical stability of blood clot and fibrinolysis, which is not shown by classical laboratory assays. This method allows for the assessment of the delicate interplay between cells and proteins in hemostasis. For platelet function testing most methods used today are based on whole blood, which prevents artifacts during the preparation of platelet rich plasma.

The implementation of near patient testing generally creates new challenges in respect to training, documentation and quality management, which are best addressed in cooperation with central laboratory functions, as long as there is mutual respect and pragmatism. Methods for quality control established in serum or plasma based clinical chemistry, are often not transferable to whole blood testing, as whole blood as a matrix is not stable for most analytes. Quality control materials provided by the manufacturers are mostly dedicated to the specific instrument and not commutable between systems, which makes standardization and proficiency testing challenging. This contributes to a generally rather high variability between whole blood coagulation tests by individual manufacturers, which has to be considered when clinical centers switch suppliers, apply literature results to their clinical practice or introduce new methods.

In spite of such challenges, the use of near patient coagulation testing has achieved guideline support and wide clinical application, and is believed to contribute to a higher clinical process quality compared to the sole application of laboratory-based coagulation testing by many clinicians and societies. The implementation of quality management, adequate training and understanding of methodological limitations can contribute to a successful use of these methods in the clinical management of coagulopathy.

POCT in molecular and genetic diagnostics

Molecular diagnostic tests are used to examine nucleic acid sequences and aid in diagnosis, prognosis or monitoring of medical conditions. The examination of the nucleic acids may consider the information on presence, quantity or location of a sequence variant, gene or genome to aid in answering a clinical question. Such methods benefit from the fact that many of the concepts, challenges and design considerations are shared whether the molecular test detects an actionable cancer variant, conducts non-invasive prenatal testing or diagnosis of an infectious disease.

Molecular genetics tests essentially deploy the three methods of hybridization, nucleic acid amplification tests (NAATs) or sequencing. These formats are not mutually exclusive and are often used in combination, especially with POCT formats. Molecular POCT formats started to be developed around 20–30 years ago using NAATs, in combination with hybridization. These formats used similar chemistries to laboratory-based tests, but were less dependent on centralized infrastructure. Such decentralized formats were driven by those working in the developing world, especially for diagnosis of infectious diseases like Tuberculosis [45]. Today there are a range of such decentralized formats allowing molecular analysis for clinical areas spanning cancer, infectious disease to pharmacogenomics. Instruments range from larger automated formats that fit into mobile laboratories, to smaller instruments potentially suitable for home testing.

There have also been alternative developments to the decentralization of NAATs. Advances in sequencing have allowed newer formats more amenable to be used outside the laboratory for nearer patient assessment [46], as well as decentralized epidemiological analysis [47]. The other development in POCT molecular testing is the use of biosensors to detect nucleic acids. Biosensors come in a range of formats that differ in sensing platform, chemistry and detection technique [48]. Biosensors arguably hold the promise of delivering what might be considered as true point of care molecular testing which are both fast and easy to use. However, today there are few commercially available biosensors nucleic acid analytical solutions. This is possibly linked to challenges with translation of such formats.

In addition to challenges with translation of molecular POCT formats, their development also arguably suffers from research standardization, along with the fact that they have to compete with high-performing established laboratory molecular tests. For example, biosensor research often uses mass or moles associated units to describe performance, whereas conventional laboratory methods tend to use nucleic acid copies of sequence, as either relative abundance or per volume unit. This makes direct comparison of analytical performance challenging. POCT formats also often deploy miniaturization and protocol simplification, which has considerable advantages when considering requirements of the specimen and its handling. However, such factors, which lend themselves to POCT, can also reduce analytical performance. Although such a tradeoff is often expected, it is rarely defined in terms of precise analytical or clinical expectations. There arguably needs to be a change in how we approach

diagnostic evaluation [48], especially when it comes to supporting development, translation and wider application of molecular POCT testing. This is needed to allow the benefits of POCT to apply to genetic testing as they do in many other areas of clinical diagnostics [49].

Global warming: why, when, how and where we should implement POCT strategies for rising oceans and weather disasters in island nations

The Earth became 1.5 °C (2.7 °F) warmer in 2023. There were 240 weather disasters worldwide. Health geographics can identify regions at risk and optimize placement of diagnostic resources. The first systematic geospatial analysis for optimal positioning of POCT resources was conducted in a remote island setting, the Bantayan Archipelago, Visayas Islands, Philippines [50]. Our goals were to perform geographic contour analysis of sea and land ambulance rescue times in the archipelago; to design point-of-care strategies for medical emergencies and weather disasters made more intense by global warming and rising oceans; to select critical care test clusters for rapid response, mobility, and improved community access; to implement mobile tuberculosis screening with artificial intelligence-enhanced low exposure X-ray and portable molecular diagnostics; and to assess needs for prehospital testing, including mobile vans on spatial care paths that accelerate decision making, increase efficiency, improve outcomes, and enhance standards of care. We performed needs assessment, inspected healthcare facilities, and collected ambulance rescue times from Emergency Medical Services professionals responsible for sea and land rescue in the Bantayan Archipelago. We considered environmental factors that affect reagent supplies and instrument operation on ambulances [51–53]. We mapped sea and land ambulance rescue routes and time contours. To reveal gaps, we statistically compared fastest and slowest patient rescue times from islands, islets, and barangays to the District Hospital on Bantayan Island. We developed spatial care paths (the fastest routes to care) for acute myocardial infarction, community crises, and infectious diseases. We generated a compendium of prehospital diagnostic testing, integrated outcomes evidence, and synthesized diagnostic needs and public health goals to recommend POC strategies that build geographic health resilience by accelerating diagnosis, speeding triage, expediting rescue, facilitating treatment, and balancing ambulance vs. ER workload [54]. We observed limited access to Coronavirus disease 2019 (COVID-19) assays, absence of blood gas/pH testing for critical care support, and spatial gaps in land and airborne rescues that worsened during inclement weather and sea swells. Mean paired differences (slowest-fastest) in ambulance rescue times to the District Hospital on Bantayan Island for both islands and barangays were significant ($p<0.0001$). Spatial care path analysis showed an interventional cardiologist should be available at the Bantayan District Hospital. Referrals to Cebu City Heart Centers encounter prohibitive delays. Geospatial strengths comprised distributed primary care that can be facilitated by POCT, logical interisland transfers for which decision making and triage could be accelerated with onboard diagnostics, and healthcare networks amenable to medical advances in prehospital testing that accelerate treatment. POCT should be positioned upstream close to homes and populations that have prolonged rescue time contours [55, 56]. Point-of-care strategies will decrease disparities in mortality among archipelago vs. Cebu City urban dwellers, help improve island public health, enhance resilience for increasingly adverse and frequent climate change weather disasters that impact highly vulnerable coastal areas, and assist the coastal communities at risk in preparing for rising oceans, community isolation, forced relocation, and weather disasters like super typhoons.

POCT and evidence-based laboratory medicine (EBLM) does it leverage any advantage in clinical decision making?

Evidence-based Laboratory Medicine (EBLM) is a distinct branch of evidence-based medicine (EB) which focuses on evaluation of laboratory tests impact, with an overall aim of improving patient outcomes. Studies on POCT issue mostly report analytical performances (central laboratory vs. POCT) which are usually acceptable but do not report patient outcomes assessment [57]. This is probably because the use of POCT devices implicates a shift in diagnostic practice across all health organizations, and this aspect is extremely hard to be measured and, consequently, generate evidence. POCT as a diagnostic tool to fulfill the unmet clinical need by central laboratory is now an emerging issue due to consolidation policies. What is the unmet clinical need resolved by POCT that cannot be answered by a central laboratory? What is the clinical pathway where POCT is employed? Which are the POCT expected test benefits compared to central laboratory testing? And who are the POCT stakeholders? These questions may be both important in the clinical practice as well in EBLM evaluations.

The development of a value proposition for POCT medical testing requires precise and clear definition of the clinical patient presentation, test impact as outcomes and the setting of care. The main aim is the appraisal of how POCT test results improve clinical decision-making and patients, thus promoting efficacy and efficiency in the entire health-care process. In this complex and challenging analysis, recognized useful methodology may be proposed as GRADE (grading of recommendations assessment, development, and evaluation), that is a systematic and explicit approach to grading the quality of evidence and the strength of recommendations related to the diagnostic test as valuable healthcare intervention. An example is the NICE (National Institute for Health and Care Excellence) Guidelines NG 237 "suspected acute respiratory infection over 16s: assessment at first presentation and initial management. Evidence reviews for rapid test to inform triage and antibiotic prescribing decisions", released in 2023 [58]. In these guidelines, outcomes such as hospital mortality, escalation of care, antibiotic and antiviral drug use and others were evaluated. After a systematic review, the results evidenced the POCT C-reactive protein (CRP) test compared with the usual care had no effect on mortality, increased the re-consultation risk but reduced the initially prescribed antibiotics, thus finally making CRP POCT a potentially cost-effective approach. It is noteworthy that a study evaluating the antibiotic prescription in six UK sites after the introduction of CRP POCT compared to the usual care showed a decrease of 20 % in prescription in five sites, a decrease of 60 % in one site and no effects in the remaining. To this end, if recommendations based on evidence proposed by healthcare institutions or scientific societies on an international or national basis are fundamental to promote an EBLM, it is important to translate the suggested recommendation to a local setting of care, taking in account the local professional culture and clinical organization. The presence of a local Board of POCT is of value to promote the clinical governance, and medicine laboratory department may endorse a leadership to evaluate unmet clinical needs by local central or current networking laboratories, the clinical application and meaning of POCT test results and to define risk management policies to reduce the clinical risk. It is also a duty of the laboratory to select the best technologies to implement the POCT, to define the general quality procedures (QCs and QIs) and to implement educational programs and audits for POCT personnel and clinicians.

Artificial intelligence as an integration tool

Within the healthcare system, patients generate a substantial amount of data daily. These include data from laboratory results, diagnostic images, medications, medical visits, etc. Recently, self-collected data such as those obtained from wearable devices or POCT results, have been suggested to be useful in improving patient care, particularly in future applications using machine learning (ML) or AI tools [59]. However, all these sources of data are not easily integrable. This is due to differences in data types (structured vs. unstructured) and the need for extensive transformation and standardization. These obstacles hinder real-time integration, reinforcing data silos and reducing access to useful clinical information.

Standardizing or harmonizing results can promote a more cohesive approach to future data management, thereby reducing potential fragmentation. In clinical laboratories, in addition to test results, a significant amount of information is generated daily throughout the entire testing process [60]. This information encompasses test names, audit trail modifications, and technical or medical validations, as well as clinical wards for inpatients, the general practitioner reference for outpatients, and other details or information of relative importance. However, most laboratory information systems (LIS) can record only part of this information. Total testing process additional data could enhance data reliability and interchange of tests by incorporating useful information for sharing and integrating results. Finally, the LIS architecture is specifically designed to prioritize security; however, it may lack flexibility when dealing with various data types.

AI technology shows potential in integrating clinical data and assay results with modern technologies, including POCT and wearable devices. In the case of POCT, AI can be implemented to reduce the size of equipment and/or enhance the accuracy of test results. Wearable devices can be powered by new technological sensors, including chemical probes and optical and pressure sensors. These devices generate continuous data that can be used to create real-time predictions of health changes and, together with other information on patient's health status, digital twins. All these transformative scenarios required data integration and, thus, the elimination of data silos. Among them, technological infrastructure, human skills and resources, legal/privacy issues, ethical concerns, and security are some of the relevant factors. The role of clinical laboratories is to be prepared to adopt technological advancements and enhance their knowledge and competency in these areas. It is crucial to have regulatory guidelines and ethical principles in place to ensure the correct interpretation and implementation of these new technologies, without compromising privacy and security protocols and adhering to ethical guidelines.

POCT and preanalytical quality

Preanalytical quality is a cornerstone in the field of laboratory diagnostics, which includes POCT, as it plays a crucial role in ensuring accurate and reliable test results [61]. Essentially, preanalytical quality refers to all processes and procedures that take place throughout the testing process prior to the actual testing phase, including sample collection, handling, transportation and preparation. Sample collection is indeed the first critical step in pre-analytical quality, and its impact on the quality of test results is particularly high in POCT, as diagnostic testing usually takes place outside traditional laboratory boundaries, where adherence to standardized practices for sample collection and handling can be more often overlooked. In fact, the tests are usually performed by clinical staff not as trained in test performance as laboratory experts, and may also have a different level of expertise and knowledge of pre-analytical procedures. In addition, POCT testing is commonly performed using special samples (i.e., syringe containing additives and anticoagulants for enabling the analysis on whole blood), on critical patients who are in a biological condition that differs from many other patients, and who often have special sampling and analytical requirements, such as being unconscious, receiving certain therapies, or requiring repeated sampling in a fasting state and at different times. In addition, sample collection can often be more difficult than usual due to less accessible veins (or arteries), test results should be available in a shorter time, and healthcare professionals may be working under increased stress. Key quality factors in the pre-analytical phase of POCT include patient preparation errors (e.g., identification errors, inappropriate sampling time), blood collection errors (i.e., clerical errors, underfilling of blood samples), improper syringe mixing, sample handling and transportation errors (time, temperature), and unseen interferences such as hemolysis as the reference sample is usually whole blood [62, 63]. Thus, considering that POCT is commonly performed in healthcare settings located outside of direct jurisdiction and control of the laboratory, reinforced education on all potential preanalytical errors must be delivered to all healthcare professionals who have direct responsibility for performing POCT [64].

An innovative approach to quality assurance for POCTs

Testing for infectious diseases within a laboratory environment is conducted under stringent quality systems, by trained laboratory professionals under the supervision of clinical pathologists. Accreditation to ISO 15189, including participation in quality assurance (QA) is mandatory in many countries [65]. The implementation of POCT outside the laboratory has facilitated access to diagnostics for remote and regional populations, disadvantaged communities and individuals at high risk of infection [66]. POCT allows for test and treat consultations, reducing the loss to follow up and allowing immediate counseling of individuals. However, POCT is often performed by non-technical staff in resource limited facilities lacking infrastructure or technical knowledge. Although POCT are designed to be simple and robust, false test results occur [67], due to intentional or unintentional misuse of the test, equipment failure or poor testing and result management processes.

Laboratory-based QA is not fit for the purpose of POCTs. A recent review of barriers to POCT sites participating in laboratory-based QA identified several factors; (a) POCT often use different sample types to laboratory testing, (b) cost barrier to the purchase, shipping and importation of QA samples to individual sites, (c) POCT sites lack infrastructure required for QA, (d) they use fixed test dates for QA programs, and (e) a loss of QA data for comprehensive review and follow up of poor results [68]. To minimize these barriers, we proposed program modifications. Samples provided for POCT QA are inactivated and non-infectious and validated for long term storage at ambient temperature. QA samples are shipped to a local “hub” to minimize importation efforts and facilitate on-shipping to local POCT sites. These “hubs” can be ministries of health, national reference laboratories, or commercial entities. All consumables required for testing are included with the samples and access to electricity and water is not assumed.

To overcome data management issues, the National Serology Reference Laboratory, Australia (NRL) developed an internet-based QA result management system, building on the existing QC monitoring program [69]. Two types of programs were developed. Competency panels consist of a known positive and negative sample. It is recommended that a competency panel be tested at each site at least once per month but can also be used to assess the competency of new and existing staff or new deliveries of test kits. The second program is an EQAs consisting of five samples. These samples are tested without knowledge of the true test result, and the results are submitted to EDCNet. Result entry for both programs is via the scanning of a QR code provided on the panel box. To avoid fixed test events, the EQAs samples have a unique four-digit code, which identifies the true reactivity. On submission of results, the participant gets an immediate assessment of their concordance with the expected result [70]. The fit for purpose POCT QA program has since been implemented for HCV testing in remote Australian

communities as well as Scotland and Wales and in 10 African, Asian and Pacific Island nations for COVID-19 antigen testing.

The mathematics of COVID-19 rapid antigen tests – prevalence boundaries, repeat testing, and missed diagnoses

Point-of-care COVID-19 testing empowers people to be alert, manage risk, and protect elderly, family, friends, workers, and vulnerable populations. The prevalence boundary concept encourages better test performance, fewer missed diagnoses, and preparation for future crises. A prevalence boundary (PB) marks the point in prevalence where the false omission rate (R_{FO}=false negatives/(true negatives + false negatives)), exceeds the tolerance limit for missed diagnoses [71, 72]. The objectives here are to present mathematical analysis of rapid antigen test (RAgT) performance, determine why PBs are breeched, illustrate testing cycles with visual logistics, and evaluate the quantitative merits, or lack thereof, of testing three times over five days, now required by the United States Food and Drug Administration (FDA) for asymptomatic persons. The FDA also declared negative RAgT results to be only presumptive. However, both positive and negative results should be reliable. Equations were derived to graph visual logistics, compare test performance patterns, calculate PBs, and perform recursive computations [73]. An independent FDA-university-commercial evaluation of RAgTs provided repeat home testing performance data [66] used in theoretical calculations. Tiered sensitivity/specificity comprise: Tier-1) 90 %, 95 %; Tier-2) 95 %, 97.5 %; and Tier-3) 100 %, ≥99 %, respectively [74–77]. Repeating a Tier-2 test improves the PB from 44.6 to 95.2 % when R_{FO} is 5 %. In the FDA-university-commercial evaluation, RAgTs generated sensitivity of 34.4 %, which improved to 55.3 % when repeated, then 68.5 % with the third test; specificity was assumed to be 99.2 %. With R_{FO}=5 %, PBs were 7.37 , 10.46, and 14.22 %, respectively.

PB analysis indicates that, in order to avoid spreading disease with false negatives, RAgTs should achieve an initial sensitivity of at least 91.0–91.4 % [76, 77] and Tier-3 specificity of ≥99 %. When prevalence exceeds PBs, missed diagnoses can perpetuate virus transmission. We should not expect people to adopt conflicting dual performance criteria and complicated sequential protocols. Repeating low-sensitivity RAgTs three times wastes time, delays diagnosis, and defeats a fundamental purpose of POCT, i.e., rapid response. In homes, high-risk settings, and hotspots [70], PB breaches and diagnostic delays will increase risks of contagion, defeat mitigation, facilitate emergence of new variants, and transform outbreaks into prolonged endemic disease. POCT should generate rapid (not delayed), actionable (not "presumptive"), and errorless (not repeated) results along spatial care paths from homes to hospitals. Tier-3 molecular diagnostics can help avoid these harmful vicious cycles by enhancing the yield of tests performed once or twice and by minimizing missed diagnoses. Sensitivity and specificity performance metrics should be proven clinically in large independent evaluations conducted in the actual settings for which the tests are intended to be used and by the people who will use them. Clinical sensitivity and specificity performance standards for government and professional approval of POCT infectious disease tests must be set much higher, because test kits will be used in homes, communities, emergency rooms, ambulances (land, sea, and air), and other diagnostic portals, including mobile testing vans, during COVID-19 variant outbreaks and the next pandemic.

POCT networks: challenges and benefits

Serving a population of nearly 3.1 million people, the health service in Wales is provided by seven Health Boards (HB) and three specialist Trusts. The HBs are responsible for the provision of a POCT service within 15 major acute, 21 minor injury unit (MIU), 18 mental health hospitals and 30 community hospitals, along with commissioning of services to over 2,000 General practitioners. In 2006, the National POCT Delivery Group was established as an informal network of POCT managers and coordinators from across Wales as an open forum to discuss the implementation of new POCT programmes, share best practice and inform the government on quality and safety issues. Membership also included procurement and informatics experts. The group meet every 6–8 weeks and has matured over the last decade to deliver a number of specific work programmes: (i) establishment of appropriate management and governance structures within each HB; (ii) advised Government on developing a national policy on POCT which was approved and implemented in 2017; (iii) developed national training and competency documentation for POCT devices (working with qualification awarding bodies a suite of units and their associated credits were developed), (iv) developed national POCT website information resource for all healthcare providers and users; (v) developed national value-based procurement specifications and frameworks for POCT services (e.g. preferred suppliers' framework for blood gas,

pregnancy testing, urinalysis, healthcare professional blood glucose device managed service for secondary care, national formulary for patient self-testing devices for diabetes, managed service for international normalized ratio (INR) monitoring in primary care including patient self-management, a framework for viscoelastic hemostasis testing for postpartum hemorrhage, and a national procurement for POCT devices for SARS-CoV-2 antigen (Ag) testing in secondary care); (vi) developed a national POCT IT strategy and connectivity solution; e.g., a system was procured that provided the infrastructure to enable full connectivity of all approved POCT devices across Wales to support shared decision making; seven HBs, covering multiple hospital locations in both urban and rural area, and one cancer trust, have been connected representing over 3,200 devices, 35 different interfaces and a wide variety of devices; the platform was interfaced to a national LIS, facilitating integration to the patient result portal and further downstream systems; recent developments include an infrastructure design review and pilot for primary and community care connectivity; (vii) shared best practice on device evaluations such as identification and verification of candidate POCT SARS-CoV-2 Ag and antibodies tests during the pandemic and (viii) conducted national audits of the service and recommendations for improvement.

There are obvious benefits of networking, such as learning and sharing of best practices, knowledge and information resources, as well as providing help and support when needed. Financial benefits include cost effective procurement contracts due to economies of scale, improved efficiencies through standardization of devices, standardization of processes such as training and competency assessment, and working collectively to improve service delivery and a more streamlined approach for rapid deployment of a POCT service when needed. The collaborative approach, also provided a more powerful voice for POCT in Government. The disadvantage of an informal group was the inequity of resource and staff structures between HBs; service requirements differed and some did not have the capacity or resource to deliver what was needed; there was a lost opportunity to have more "joined up" services across all Wales. Scope was also limited to pathology testing for most departments and therefore imaging, respiratory, cardiac physiology devices were either not considered or there was a duplication of governance.

Building on the success of the informal network, one of the key actions in the National Pathology Programme Statement of intent, published in 2019, was to establish a more formal structured arrangement to deliver POCT in NHS Wales. A National Strategy Group of POCT clinical leads and POCT Managers from each HB, stakeholders and government representatives was established with the aim of setting the strategy and standards, with the existing National POCT Delivery Group supporting the delivery of the service. However, during the pandemic the work of the two groups was repurposed to undertake verification of candidate POCT devices/methods as part of the COVID-19 testing strategy, as well as identifying and providing advice on operational issues. In 2023, a National POCT Strategy was developed, highlighting the vision for the delivery of services along with creation of a more formal National POCT Strategy Board; a clinically led Board established to coordinate, and support the planning, implementation, and delivery of a "one Wales" POCT service that is patient focused and aligned with "Healthier Wales", which (i) delivers a "diagnostics anywhere" approach to healthcare; providing diagnostic testing where it is needed; (ii) reduces inappropriate variation using evidence-based practices consistently and transparently; (iii) facilitates efficient procurement processes for related equipment and consumables taking a value-based approach; (iv) makes efficient and effective use of workforce resources; a workforce that is flexible and can work across existing Health Board geographical boundaries; (v) ensures that workforce models are sustainable, and standardized training programmes are developed at all levels at the right level for the clinical need; (vi) embraces multidisciplinary working, breaking down the barriers between "silo" specialties, investing in advanced training of POCT teams to provide diverse and relevant skills across specialties appropriate for our future need; (vi) works in partnership with academia for opportunities, making best use of innovation with disruptive and transformational technology; and (vii) builds on the IT Strategy for future needs, making best use of business intelligence.

POCT in value-based healthcare

Value based healthcare (VBHC) is based on the equation outcome/costs. The calculation of costs should be performed on the whole cost of the process, not only on the cost of a single procedure, considering the outcome of the same process. The introduction and diffusion of POCT in clinical medicine is clearly enhanced by the possible improvement of outcome, principally due to the reduction of TAT, although the costs are usually higher than traditional analyses performed in centralized laboratories. There are few studies focused on the impact of POCT on the whole medical process; most are devoted to the analytical evaluation of instruments and methods, in comparison with traditional centralized analyses.

There are some medical processes where the use of POCT could really modify outcomes and costs, with a beneficial effect on patients: the case of over-testing possibly inducing iatrogenic anemia is an example [78]. The use of

POCT for periodical control of hemoglobin in patients hospitalized in critical areas could really decrease the volume of blood drawn and the risk of anemia.

The perception of the positive impact of POCT in all medical processes, owing to immediate reports of results and their interpretation by physicians, is not supported by specific studies. The actual utilization in daily practice involves mainly a few tests for diagnosing and monitoring diabetes, determining urinary tract and other infections, and stratifying acute cardiac syndromes. For general practitioners, many POCTs are not useful as they test chronic or rather innocuous conditions. Practitioners are unwilling to adopt technologies that are not beneficial to patient care or for the profitability of their practices. Some applications of POCT are not really decreasing the time needed for medical decision making, as reported in published papers, and actually small modifications of central clinical laboratory organization should be sufficient to answer clinicians' requests with minor costs. Conversely, in some cases clinical laboratory experts should facilitate the introduction of POCT testing, for example for direct oral anticoagulants (DOACs) testing before major surgery. Even in some specific scenarios, where POCT is generally accepted as the solution for obtaining laboratory results, in low resources healthcare (low middle-income countries, rural areas, desertification of healthcare in developed countries, disaster medicine), specific studies based on VHBC are needed, to avoid the increase of inequalities and unbalanced between beneficial effects and costs.

There is a lack of complete, comprehensive, and global evaluation of the impact of POCT in healthcare settings. Ten years ago, we selected POCT with special analytes characterized by possible high clinical impact [79]. We analyzed 84 studies for five POCT instruments: neonatal bilirubin, procalcitonin, intraoperative parathyroid hormone, cardiac troponin and blood gas analysis. Most of the articles (50 %) were studies of correlation between results obtained by using POCT instruments and those obtained with laboratory instruments. These data showed a satisfactory correlation between methods when similar analytical reactions were used. Only 13 % of the studies evaluated the impact of POCT on clinical practice. POCT decreases the time for making decisions on patient management, but the clinical outcomes have never been adequately evaluated. The scenario has not changed substantially over time, and only a minority of studies are focused on the impact on medical decisions, including an economical evaluation and cost effectiveness ratio.

The very few health technology assessment (HTA) reports on POCT are characterized by negative evaluations, because the studies are performed only on analytical or, in some cases, on preanalytical/analytical aspects, avoiding the cost and outcome impact. Moreover, the type of healthcare service organization and reimbursement by the third payer are not, in general, properly considered. Thus, studies based on randomized clinical trials and HTA reports are compellingly needed for properly evaluating the use of POCT.

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